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A comparison of rituximab and modified Ponticelli regimen (alternating steroids and cyclophosphamide) for treatment of primary membranous nephropathy

Submission date
04/04/2022

Recruitment status
No longer recruiting

Registration date
15/04/2022

Overall study status
Completed

Last Edited
23/05/2022

Condition category
Urological and Genital Diseases

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults, which is characterised by the presence of protein in the urine. There are two treatment options for this disease, both of which aim to achieve remission – the reduction of protein excretion in the urine. The modified Ponticelli regimen with cyclical steroids and cyclophosphamide is used as first-line treatment but is associated with several adverse effects such as infections, infertility and low blood cell counts. Rituximab has emerged as a newer option for treatment but it has not been compared against the modified Ponticelli regimen in head-to-head trials. The aim of this study is to assess the effectiveness of rituximab versus the modified Ponticelli regimen in inducing remission in MN.

Who can participate?
Patients aged over 18 years with primary membranous nephropathy with more than 3.5 g protein excretion in urine

What does the study involve?
Some patients can have spontaneous resolution of protein excretion in urine. Therefore all patients with primary MN will be given a 3-month observation period to watch for spontaneous resolution. Patients with severe symptoms or those with persistent protein excretion will be randomly allocated into one of the two groups and will receive either rituximab or the modified Ponticelli regimen. The rituximab group will receive two injections of rituximab on days 1 and 15. Their CD19 level (which indicates their B cell levels) will be checked at 1 and 6 months. B cells are suppressed by rituximab and a low level indicates that the rituximab was effective at suppressing the B cells. The modified Ponticelli regimen consists of alternating months of steroids and cytotoxic agents for a total of 6 months. Steroids are given in months 1, 3 and 5 which will include three injections of methylprednisolone on days 1-3 followed by prednisolone tablets. Cyclophosphamide tablets will be given in months 2, 4 and 6.

What are the possible benefits and risks of participating?
The participants would receive two treatments that are routinely being used for this disease. All drugs used in this study have an established role in treatment of MN and all are associated with specific side effects. Steroids can cause weight gain, high blood sugar, bone weakness, muscle wasting and an increased risk of infections. Cyclophosphamide can cause infections, infertility, bladder problems, low blood counts as well as cancer. Rituximab is typically associated with reactions during infusion including flushing, itching and sometimes low blood pressure.

Where is the study run from?
Muljibhai Patel Urological Hospital, Nadiad (India)

When is the study starting and how long is it expected to run for?
June 2018 to June 2021

Who is funding the study?
Muljibhai Patel Society for Research in Nephrology, Nadiad, Gujarat (India)

Who is the main contact?
Dr Sandhya Suresh
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Contact information

Type(s)
Principal investigator

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Additional identifiers

Protocol serial number
525

Study information

Scientific Title

INdian COntrolled trial of RITuximab vs Modified Ponticelli regimen for treatment of primary membranous nephropathy

Acronym
INCORIT-M

Study objectives
Rituximab is non-inferior to modified Ponticelli regimen in inducing remission (complete or partial) at 6 months in patients with primary membranous nephropathy (PMN).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 16/08/2018, Muljibhai Patel Society for Research in Nephro-Urology Ethics Committee (Muljibhai Patel Urological Hospital, Dr. Virendra Desai Road, Nadiad - 387001, Gujarat, India; +91 (0)268 2520330; info@mpuh.org), ref: EC/525/2018

Primary study design
Interventional

Study design
Interventional randomized controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Primary membranous nephropathy

Interventions
Intervention arm - Rituximab injection 500mg IV given on days 1 and 15
Control arm - Modified Ponticelli regimen (cyclical steroids/cyclophosphamide for 6 months)

Months 1, 3 and 5: 1 g IV methylprednisolone daily (Days 1–3), then oral prednisolone (0.5 mg/kg /day) for 27 days (Days 4–30).
Months 2, 4 and 6: Oral cyclophosphamide (2.0 mg/kg/day) for 30 days.

The researchers used a random number-producing algorithm for block randomisation using sealed envelope online software. Randomisation and treatment allocation were then done by the primary investigator using this randomisation list in a concealed manner in a 1:1 manner using sealed envelopes.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Rituximab, cyclophosphamide, steroids

Primary outcome(s)
The proportion of patients reaching complete or partial remission at 6 months, defined according to the 2012 KDIGO guidelines as follows:
Complete remission: a reduction of proteinuria to <0.3 g/24 h (uPCR <300 mg/g) with normal serum albumin concentration and normal serum creatinine
Partial remission: a reduction of proteinuria to <3.5 g/day (uPCR <3500 mg/g) and a 50% or greater reduction from peak values accompanied by an improvement or normalisation of serum albumin concentration and stable serum creatinine
1. Proteinuria measured using the urine protein creatinine ratio (using Pyrogallol red and Jaffe kinetic reaction test methodology) at baseline and 6 months
2. Serum albumin concentration measured using the Bromocresol green test at baseline and 6 months
3. Serum creatinine measured using the Jaffe kinetic test at baseline and 6 months

Key secondary outcome(s)
1. The proportion of patients reaching either complete or partial remission at 12 months after therapy (measured as per the primary outcome measure)
2. The proportion of patients with relapsing nephrotic syndrome measured among patients who previously underwent partial remission or complete remission at any time during the study period as determined by proteinuria (measured as per the primary outcome measure)
3. The time to relapse of nephrotic syndrome after initial remission as determined by proteinuria (measured as per the primary outcome measure)
4. Serum anti-PLA2R levels measured using EUROIMMUN Anti-PLA2R ELISA (quantitative method) before treatment and at 6 and 12 months post-therapy
5. Efficacy outcome variables during the study period including the trend of the magnitude of proteinuria, serum albumin, serum proteins, serum creatinine and estimated GFR (measured by the CKD-EPI formula) at baseline, 6 and 12 months
6. Proportion of patients developing the following adverse events during the study period, as determined by clinical evaluation including patient interviews and patient notes and lab investigations:
6.1. Infections: symptoms such as fever, cough, dysuria; signs of infection such as fever, respiratory system signs including rales/crepitations, skin lesions of Tinea; lab investigations including total white blood cell (WBC) count (by automated cell counter machine), urine routine analysis (using Multistix and microscopic examination of urine sediment after centrifugation), chest X-ray
6.2. Leucopenia determined by total WBC count (by automated cell counter machine)
6.3. Infusion reaction determined by clinical evaluation
6.4. Acute kidney injury after the start of therapy determined by measuring serum creatinine using the Jaffe kinetic reaction

Completion date
30/06/2021

Eligibility

Key inclusion criteria
1. Patients older than 18 years who provide written informed consent.
2. Biopsy-proven primary MN within 2 years of enrolment with nephrotic range proteinuria denoted by 24-hour urine protein ≥3.5 g or UPCR (urine protein:creatinine ratio) ≥3500 mg/g as well as the following:

2.1. Serology or biopsy positive for AntiPLA2R
2.2. Serology or biopsy negative for AntiPLA2R and secondary causes ruled out
2.3. Evaluation for secondary causes was done in all patients, even in patients who were positive for Anti-PLA2R antibodies on serology or PLA2R antigen on biopsy because these have also been found in some cases of secondary MN
3. Estimated GFR ≥30 ml/min/1.73m². The CKD-EPI creatinine equation was used for the calculation of the eGFR
4. Treatment with an ACEI or ARB for at least 3 months before enrolment

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
68

Key exclusion criteria
1. Secondary MN
2. Active serious infections
3. Pregnant women
4. Suspected or known hypersensitivity to either interventional drug
5. Patients with persistently low estimated GFR <30 ml/min/1.73m² in the absence of acute causes such as acute tubular injury, renal vein thrombosis and others

Date of first enrolment
26/08/2018

Date of final enrolment
03/10/2020

Locations

Countries of recruitment
India

Study participating centre
Muljibhai Patel Urological Hospital
Dr. Virendra Desai Road

Nadiad
India
387001

Sponsor information

Organisation
Muljibhai Patel Urological Hospital

ROR
https://ror.org/059h1d250

Funder(s)

Funder type
Research organisation

Funder Name
Muljibhai Patel Society for Research in Nephro-Urology

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the subsequent results publication

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet			05/04/2022	No	Yes
Protocol file			12/04/2022	No	No